Abstract: Oral malignant melanoma is a rare aggressive neoplasm of melanocytic origin, usually found on the hard palate and gingiva, and representing 0.2-8% of all melanomas. Unfortunately, oral mucosal melanomas have by far the worst prognosis, and therefore early detection is indispensable for improving their prognosis. Histopathological examination of any pigmented lesion is essential to rule out this lethal entity. Computed tomography is of help for assessing both the extent of the lesion and the presence of regional metastasis to the lymph nodes. Malignant melanoma cells stain positively with antibodies against HMB-45, S-100 protein and vimentin, and so immunohistochemistry can play a crucial role in evaluating the depth of invasion and location of metastasis. The presence of satellite/in transit lesions is an important factor affecting prognosis. Here we report a 30-year-old female patient with malignant melanoma of the maxillary gingiva and palate associated with a satellite lesion, highlighting the role of various diagnostic tools in its detection, and the prognosis associated with satellitism. (J Oral Sci 53, 239-244, 2011)

Keywords: malignant melanoma; melanocytes; immunohistochemistry; satellite lesion.

Introduction
Melanoma is a neoplasm of epidermal melanocytes. It is one of the most biologically unpredictable and deadly of all human neoplasms (1). Primary oral malignant melanoma is uncommon, usually with a relatively short evolution, ranging from a few months to a few years. Oral melanomas are known to have the worst prognosis, but early diagnosis and treatment can help to reduce the mortality rate (2). The prognosis is closely related to tumor thickness, occurrence of any satellite lesion, and regional and distant metastasis, which is evident in 50% of patients at presentation. It is difficult to assess the extent of malignant melanoma, but treatment and prognosis depend on an accurate assessment of the extent of disease and the presence or absence of metastasis, such as to regional lymph nodes. Biopsy of any suspicious pigmented lesion is important for confirming the diagnosis, and immunohistochemistry can be useful for locating occult tumor cells in tissue sections, thus assisting evaluation of the depth of invasion and detection of metastasis. Here we report a 30-year-old female patient with malignant melanoma of the maxillary gingiva and palate associated with a satellite lesion, emphasizing the role of various diagnostic modalities in detection and treatment planning.

Case Report
A female patient aged 30 years presented at the department of oral medicine and radiology with a black-colored growth on the anterior maxilla that had been present for 4 months. The patient had first noticed blackish discoloration of the gingiva during her pregnancy 2 years previously, but this has gradually increased in size during...
the preceding 4 months. Bleeding from the same region on tooth-brushing had been evident for 3 months. There was no relevant medical or family history. Oral examination revealed a bluish-black exophytic growth on the right side of the maxillary gingiva and palate in the anterior region, extending antero-posteriorly from the canine to the second premolar region and from the marginal gingiva to the vestibular sulcus superiorly, measuring 3.5 × 2 cm (Fig. 1a). The lesion crossed the interdental region extending palatally from the gingival margin of the right maxillary incisor to the second premolar and up to the anterior aspect of the hard palate (Fig. 1b). The left maxillary central incisor was missing and the patient wore a removable partial denture. The growth was soft in consistency and non-tender, and bleeding on probing was present. Two submandibular lymph nodes on both the left and right sides were palpable, firm to hard in consistency, and fixed to the underlying structures. On the basis of the history and the clinical examination, a provisional diagnosis of oral malignant melanoma was considered.

Routine blood investigations showed values within the normal ranges. An intraoral periapical radiograph of the region from the maxillary right canine to the second premolar showed mild bone destruction. A chest X-ray was negative for metastasis. Ultrasound examination of the neck revealed bilateral enlarged submandibular lymph nodes, the largest measuring 38 mm on the right side. Axial CT scan revealed a heterogeneous hyperdense space-occupying lesion measuring approximately 4.2 × 3 × 2.7 cm in the right gingivo-labial sulcus. This lesion had eroded the alveolar process of the maxilla on the right side, but the integrity of the hard palate was maintained (Fig. 2a). On administration of a contrast agent, mild homogeneous enhancement was evident, and multiple lymph nodes measuring approximately 3-4 cm were seen bilaterally in the submandibular and deep cervical (jugulomohyoid) region. Peripheral ring enhancement was also evident on contrast images, being suggestive of central necrosis in the lymph nodes (Fig. 2b).

Fine-needle aspiration cytology of the lesion and right

Fig. 1 Labial (a) and palatal (b) lesion of malignant melanoma.

Fig. 2 Axial CT scan depicting erosion of the alveolar process on the right side (a; arrow) and necrosis of the cervical lymph nodes (b; arrow).
submandibular lymph node was done and smears showed little cellularity and a few isolated cells, as well as clumps of epithelial cells. Many cells were laden with brownish pigment granules, and showed mild pleomorphism and anisonucleosis (Fig. 3), suggestive of malignant melanoma. Incisional biopsy was carried out for confirmation, and histopathological examination revealed numerous atypical melanocytes with or without melanin pigment in the connective tissue. Well vascularized tumor tissue extensively infiltrated by sheets and nests of large cells with pleomorphic nuclei, prominent nucleoli and abundant cytoplasm with brown pigment, confirmed the diagnosis of malignant melanoma (Fig. 4). Immunohistochemical analysis demonstrated that the tumor cells had strong, diffuse, granular cytoplasmic reactivity for HMB-45 (Fig. 5a), S-100 protein (Fig. 5b) and vimentin (Fig. 5c), thus strongly supporting the diagnosis of malignant melanoma.

Fig. 3 FNAC section showing many cells laden with brownish pigment granules.

Fig. 4 Histopathological section showing numerous atypical melanocytes in the connective tissue (a and b).

Fig. 5 Immunoreactivity for HMB-45 (a), S-100 protein (b) and vimentin (c).
The patient was referred to J.K. Cancer Institute for management, where she was treated with dacarbazine 200 mg/day (day 1 to day 5), cisplatinum 50 mg/day, intravenously (day 1 to day 3), and temozolomide 250 mg/day (day 6 to day 10). Mild reduction in the size of the lymph nodes was seen after chemotherapy, and surgery was planned. However, the patient did not continue the treatment, and 4 months later she revisited the department and was found to have a black-colored macule 0.5 cm in diameter on the left side of the anterior hard palate, which was considered to represent satellitism (Fig. 6). The patient was encouraged to undergo regular treatment, but later was lost to follow-up.

Discussion

Melanoma is a malignant neoplasm of melanocytic origin that arises from a benign melanocytic lesion or de novo from melanocytes within otherwise normal skin or mucosa. Melanocytes are neural crest-derived cells that during embryologic development, migrate from the neural crest into the epithelial lining of the skin and, in the developed skin, reside primarily in the basal epithelial layer (2). The function of melanocytes in the mucosa is not fully understood, but their presence in the basal layer of the epithelium is well known. Variations in the density of melanocytes are seen in different parts of the body, and in the gingival epithelium the ratio of melanocytes to basal keratinocytes is 1 : 15 (3). Because the oral cavity develops from an ectodermal depression or invagination, the epithelial lining of the oral mucosa, similarly to skin, normally contains melanocytes in its basal layer, which can differentiate into melanoma as is the case in the skin (2).

The incidence of mucosal melanoma is lower than in the skin. Jackson and Simpson (4) have indicated that malignant melanoma of the oral cavity represents less than 2% of all melanomas, and Reddy et al. have indicated an incidence of 0.4-1.3%. According to studies from India, about 16% of melanomas have been noted intraorally (5). This malignancy is a lesion of adulthood, and rarely identified in patients under the age of 20 years, the highest incidence being reported in the fifth decade (4). Males appear to be affected more often than females, and whites more than blacks.

The etiology of oral melanoma is unknown. Exposure to sunlight, denture irritation, chewing tobacco with betel nut and smoking have been implicated as etiologic factors in the past. However, there has been no evidence to support these theories (6). Currently, most oral melanomas are thought to arise de novo (1). The most common site of involvement is the hard palate and maxillary gingiva, but other oral sites include the mandible, tongue, buccal mucosa, and upper and lower lips. There is no apparent explanation as to why oral melanomas show a predilection for occurrence in the maxilla. Symptoms of oral melanomas vary, and may include a bleeding lump and, rarely, pain (6). The so-called ABCDE rule summarizes the clinical features of oral malignant melanomas: Asymmetry, in which one half does not match the other, Border irregularity, with blurred, notched or ragged edges, Color irregularity, with non-uniform pigmentation, including brown, black, tan, red, white or blue, Diameter greater than 6 mm, growth in itself being a sign, and Elevation, a raised surface also being a sign (1). Unfortunately, these symptoms appear relatively late in the course of the disease, by which time significant vertical invasion of the tumor cells into the underlying tissues has already occurred. Rolled borders are not a frequent feature of oral mucosal melanoma because the atypical melanocytes exhibit a pagetoid mode of spread, resulting in uniform epithelial thickening (6). Oral melanomas can be classified into five types, based on the clinical appearance: pigmented nodular, non-pigmented nodular, pigmented macular, pigmented mixed, and non-pigmented mixed.

Widespread metastasis is a well known feature of malignant melanoma. Metastases to regional lymph nodes and distant spread to bone are encountered in end-stage patients. Extensive destruction of the underlying bone is also present in 78% of patients. The presence of satellite, smaller structures or lesions, and metastatic melanoma in the skin adjacent to the primary tumor is known as satellitosis. Microsatellites are discrete tumor nests exceeding 0.05 mm in diameter that are separated from
the main body of the tumor by normal reticular dermal collagen or subcutaneous fat. This phenomenon has been observed quite often in cutaneous melanomas, but rarely in the oral cavity (7). In the present case, the appearance of a macule on the left side of the hard palate, 4 months after the patient had first presented, indicated the emergence of satellitosis. The presence of satellitism around the main lesion could have been due to embolic spread of the tumor along the lymphatics, with the development of secondary tumors. This would likely indicate a poor prognosis.

Histopathological examination in the present case showed all the typical features of malignant melanoma. Immunohistochemistry has been shown to be an effective adjunct to histopathological diagnosis through the establishment of a definitive diagnosis or through confirmation of hematoxylin and eosin (HE) staining. Malignant melanomas are reactive for HMB45, S-100 protein and vimentin. Staining for these antigens may also be useful for locating occult tumor cells in tissue sections, aiding in the evaluation of depth of invasion and detection of metastasis (8). In the present case also, tumor sections were highly reactive for these immunohistochemical markers. Tanaka et al. have suggested that the biologic behavior of melanoma may be associated with the expression of Rb, pRb2/p130, p53 and p16 proteins, which may be helpful for diagnosis of this neoplasm (9).

Computed tomography demonstrates malignant melanoma as an expansile, homogeneously enhanced mass. This modality is helpful for assessing the extent of the lesion and exploring regional metastasis to the lymph nodes (10). In our patient also, a space-occupying lesion was seen in the gingivo-labial sulcus. On administration of contrast, multiple lymph node enlargement was seen bilaterally in the submandibular and deep cervical region. These lymph nodes exhibited peripheral ring enhancement, which was suggestive of central necrosis. The presence of metastasis from malignant melanoma can be established on the basis of its unique MR characteristics. Melanin has paramagnetic properties that can affect the signal on MR images, giving melanotic melanomas a characteristic intensity pattern. They appear hyperintense on T1-weighted sequences and intermediate to hypointense on T2-weighted sequences (10). Surgery is the first choice of treatment. Radiotherapy has been used successfully in the early stages, whereas chemotherapy has achieved a relatively low response rate. Oral melanomas have a poorer prognosis than cutaneous melanomas, with a five-year survival rate of 15% (3).

Early detection and treatment are mandatory for better prognosis of this lethal entity. A careful and thorough examination of the oral cavity and biopsy of any growing pigmented lesion is essential to rule out malignant melanoma of the oral cavity. Any pigmented lesion in the oral cavity should be closely followed up. The presence of a satellite lesion around the main lesion might be an indicator of poor prognosis. Earlier identification of oral melanotic lesions simplifies treatment and greatly improves the prognosis. The use of advanced diagnostic methods such as immunohistochemistry can definitely aid evaluation of the depth of invasion as well as the detection of metastases.

Acknowledgments

We would like to thank Dr. Radhika Bhavle, Professor and H. O. D, Department of Oral Pathology, Krishna-devaraya College of Dental Sciences & Hospital, Bangalore, for giving her expert opinion about the histopathological sections.

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